

CLAIMS

1. A method for promoting auto-induction of transcription of cloned DNA in cultures of bacterial cells grown batchwise, said transcription being under the control of a promoter whose activity can be induced by an exogenous inducer whose ability to induce said promoter is dependent on the metabolic state of said bacterial cells, the method comprising:
  - a) providing a culture medium comprising:
    - i) an inducer that causes induction of transcription from said promoter in said bacterial cells;
    - ii) a metabolite that prevents induction by said inducer, the concentration of said metabolite being adjusted so as to substantially preclude induction by said inducer in the early stages of growth of the bacterial culture but such that said metabolite is depleted to a level that allows induction by said inducer at a later stage of growth, and
  - b) inoculating the culture medium with a bacterial inoculum, the inoculum comprising bacterial cells containing cloned DNA, the transcription of which is induced by said inducer; and
  - c) incubating the culture of step b) under conditions appropriate for growth of the bacterial cells.
2. The method of Claim 1 wherein the bacterial cells are Escherichia coli cells.
3. The method of Claim 2 wherein the Escherichia coli cells are BL21(DE3).
4. The method of Claim 1 wherein the cloned DNA is carried in a plasmid expression vector.

5. The method of Claim 4 wherein the plasmid expression vector carries a T7lac promoter.
6. The method of Claim 1 wherein the promoter whose activity is induced by an exogenous inducer is repressed by the *lac* repressor.
7. The method of Claim 6 wherein the promoter whose activity is induced by an exogenous inducer is selected from the group consisting of a *lac* promoter, a *lacUV5* promoter and a T7lac promoter.
8. The method of Claim 1 wherein the exogenous inducer is lactose.
9. The method of Claim 1 wherein the metabolite is glucose.
10. The method of Claim 1 wherein the metabolite is selected from the group consisting of glucose and amino acids.
11. The method of Claim 1 wherein the culture medium further comprises a complex mixture of nutrients selected from the group consisting of yeast extract and a tryptic digest of casein.
12. The method of Claim 1 wherein the culture medium further comprises carbon sources that can be utilized by bacterial cells in the culture without preventing induction by the exogenous inducer.
13. The method of Claim 12 wherein the carbon sources are selected from the group consisting of glycerol, succinate, fumarate, malate, citrate, acetate, maltose and sorbitol.

14. The method of Claim 1 wherein the culture medium further comprises from about 0.5 mM to about 10 mM magnesium cation.
15. The method of Claim 1 wherein the culture medium further comprises from about 0.05x to about 2x metals mix.
16. The method of Claim 1 wherein the culture medium further comprises from about 5 mM to about 200 mM phosphate anion.
17. The method of Claim 1 wherein the culture medium further comprises from about 0.5 mM to about 25 mM sulfate anion.
18. The method of Claim 1 wherein the culture medium further comprises from about 20 mM to about 100 mM ammonium cation.
19. The method of Claim 1 wherein the culture medium further comprises from about 5 mM to about 200 mM sodium cation.
20. The method of Claim 1 wherein the culture medium further comprises from about 5 mM to about 200 mM potassium cation.
21. The method of Claim 1 wherein the culture medium comprises components such that the culture after growth to saturation has a pH between about pH 4.5 and about pH 9.5.
22. The method of Claim 21 wherein the culture after growth to saturation has a pH preferably between about pH 5.5 and about pH 7.5.

23. A method for improving the production of a selenomethionine-containing protein or polypeptide in a bacterial cell, the protein or polypeptide being produced by recombinant DNA techniques, the bacterial cell encoding a vitamin B12-dependent homocysteine methylase, the method comprising culturing the bacterial cell in a culture medium containing vitamin B12.
24. The method of Claim 23 wherein the bacterial cell is an *Escherichia coli* cell.
25. The method of Claim 23 wherein the culture medium further comprises from about 0.5 mM to about 10mM MgSO<sub>4</sub>.
26. The method of Claim 23 wherein the culture medium further comprises from about 0.05x to about 2x metals mix.
27. The method of Claim 23 wherein the culture medium further comprises from about 0.05x to about 2x metals mix, from about 5 mM to about 200 mM phosphate anion, from about 0.5 mM to about 25 mM sulfate anion, and from about 20 mM to about 100 mM ammonium cation.
28. The method of Claim 23 wherein the culture medium further comprises from about 75 to about 150 µg/ml Se-Met.
29. The method of Claim 23 wherein the culture medium is PASM-5052.
30. A method for suppressing transcription of cloned DNA in cultures of bacterial cells grown batchwise, said transcription being under the control of a promoter whose activity can be induced by an exogenous inducer whose ability to induce said promoter is dependent on the metabolic state of said bacterial cells, the method comprising:

- a) providing a culture medium comprising a carbon source whose uptake and metabolism by said bacterial cells suppresses induction of transcription from said promoter;
  - b) inoculating the culture medium with a bacterial inoculum, the inoculum comprising bacterial cells containing cloned DNA, the transcription of which is suppressed by the carbon source; and
  - c) incubating the culture of step b), with shaking, under conditions appropriate for growth of the bacterial cells.
31. The method of Claim 30 wherein the bacterial cells are *Escherichia coli* cells.
32. The method of Claim 30 wherein the cloned DNA is carried in a plasmid expression vector.
33. The method of Claim 30 wherein the promoter whose activity is repressed by the endogenous repressor is selected from the group consisting of a *lac* promoter, a T7/*lac* promoter and a *tac* promoter.
34. The method of Claim 30 wherein the endogenous repressor is the *lac* repressor.
35. The method of Claim 30 wherein the carbon source is glucose.
36. The method of Claim 30 wherein the glucose concentration ranges from about 0.25% to about 2.0%.
37. The method of Claim 30 wherein the culture medium further comprises from about 0.5 mM to about 10mM MgSO<sub>4</sub>.
38. The method of Claim 30 wherein the culture medium further comprises from about 0.05X to about 0.15X metals mix.

39. The method of Claim 30 wherein the culture medium is selected from the group consisting of: P-0.5G, PA-0.5G, ZYP-0.8G, and NIMS.
40. The method of Claim 1 wherein the culture medium is selected from the group consisting of: ZYP-5052, PA-5052, P-5052, PASM-5052, MAS-15052, MS-15052 and ZYM-15052.